



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/11, A61K 31/70, C12Q 1/68, C12N 15/86, G01N 33/68, C07H 21/00, C12Q 1/26		A3	(11) International Publication Number: WO 98/05769 (43) International Publication Date: 12 February 1998 (12.02.98)
(21) International Application Number: PCT/CA97/00540 (22) International Filing Date: 1 August 1997 (01.08.97) (30) Priority Data: 60/023,040 2 August 1996 (02.08.96) US 60/039,959 7 March 1997 (07.03.97) US (71) Applicant (for all designated States except US): GENESENSE TECHNOLOGIES, INC. [CA/CA]; 100 Olivia Street, Winnipeg, Manitoba R3E 0V9 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): WRIGHT, Jim, A. [CA/CA]; 15 Bryn Mawr Road, Winnipeg, Manitoba R3T 3K8 (CA). YOUNG, Aiping, H. [CA/CA]; 717 Pacific Avenue, Winnipeg, Manitoba R3E 1G1 (CA). (74) Agent: BERESKIN & PARR; 40th floor, 40 King Street West, Toronto, Ontario M5H 3Y2 (CA).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 25 June 1998 (25.06.98)	
(54) Title: ANTITUMOR ANTISENSE SEQUENCES DIRECTED AGAINST R1 AND R2 COMPONENTS OF RIBONUCLEOTIDE REDUCTASE (57) Abstract Compounds and methods for modulating cell proliferation, preferably inhibiting the proliferation of tumor cells are described. Compounds that may be used to modulate cell proliferation include inhibitors of ribonucleotide reductase expression, that is, inhibitors of transcription or translation of the gene encoding ribonucleotide reductase. Antisense oligonucleotides complementary to regions of ribonucleotide reductase gene are particularly useful inhibitors.			

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00540

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/11 A61K31/70 C12Q1/68 C12N15/86 G01N33/68
C07H21/00 C12Q1/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N A61K C12Q G01N C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BJÖRKLUND S ET AL: "S-PHASE-SPECIFIC EXPRESSION OF MAMMALIAN RIBONUCLEOTIDE REDUCTASE R1 AND R2 SUBUNIT MESSENGER RNAS." BIOCHEMISTRY 29 (23). 1990. 5452-5458. CODEN: BICAW ISSN: 0006-2960, XP002053156	1-6
Y	---	10-18
X	N. PAVLOFF ET AL.: "Sequence analysis of the large and small subunits of human ribonucleotide reductase." DNA SEQUENCE, vol. 2, 1992, pages 227-234, XP002048232 see the whole document	1-6
Y	---	10-18
	--- -/-	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

26 January 1998

Date of mailing of the international search report

07.05.98

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hix, R

INTERNATIONAL SEARCH REPORT

In .ational Application No

PCT/CA 97/00540

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. THELANDER ET AL.: "Isolation and characterization of expressible cDNA clones encoding the M1 and M2 subunits of mouse ribonucleotide reductase." MOLECULAR AND CELLULAR BIOLOGY, vol. 6, no. 10, October 1986, pages 3433-3442, XP002053157	1-6
Y	see the whole document ---	10-18
X	M. THELANDER ET AL.: "Molecular cloning and expression of the functional gene encoding the M2 subunit of mouse ribonucleotide reductase: a new dominant marker gene." THE EMBO JOURNAL, vol. 8, no. 9, 1989, pages 2475-2479, XP002053158	1-6
Y	see the whole document ---	10-18
X	M.M. CHAUDHURI ET AL.: "cDNA sequence of the small subunit of the hamster ribonucleotide reductase." BIOCHEMICA ET BIOPHYSICA ACTA, vol. 1171, 1992, pages 117-121, XP002053159	1-6
Y	see the whole document ---	10-18
X	BARKER R H JR ET AL: "Inhibition of Plasmodium falciparum malaria using antisense oligodeoxynucleotides." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 93 (1). 1996. 514-518. ISSN: 0027-8424, XP002053162	1,2
Y	see the whole document ---	3-6, 10-18
X	CHAKRABARTI, DEBOPAM ET AL: "Cloning and characterization of subunit genes of ribonucleotide reductase, a cell-cycle-regulated enzyme, from Plasmodium falciparum" PROC. NATL. ACAD. SCI. U. S. A. (1993), 90(24), 12020-4 CODEN: PNASA6;ISSN: 0027-8424, 1993, XP002053163	1-3
Y	see the whole document ---	4-6, 10-18

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INTERNATIONAL SEARCH REPORT

II. National Application No

PCT/CA 97/00540

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STANDARD N ET AL: "MATERNAL MESSENGER RNA FROM CLAM OOCYTES CAN BE SPECIFICALLY UNMASKED IN-VITRO BY ANTISENSE RNA COMPLEMENTARY TO THE 3'-UNTRANSLATED REGION." GENES DEV 4 (12A). 1990. 2157-2168. CODEN: GEDEEP ISSN: 0890-9369, XP002053164	1,2
Y	see the whole document	3-6, 10-18
X	--- STANDART N ET AL: "CONTROL OF TRANSLATION OF MASKED MRNAS IN CLAM OOCYTES." ENZYME (BASEL) 44 (1-4). 1990 (1991). 106-119. CODEN: ENZYBT ISSN: 0013-9432, XP002053165	1,2
Y	see the whole document	3-6, 10-18
P,X	--- HUANG A ET AL: "Ribonucleotide reductase R2 gene expression and changes in drug sensitivity and genome stability." CANCER RESEARCH 57 (21). 1997. 4876-4881. ISSN: 0008-5472, XP002053166	1-6, 10-18
P,X	--- MADER R M ET AL: "Transcription and activity of 5-fluorouracil converting enzymes in fluoropyrimidine resistance in colon cancer in vitro." BIOCHEMICAL PHARMACOLOGY 54 (11). 1997. 1233-1242. ISSN: 0006-2952, XP002053167	1-6, 10-18
A	--- R.A.R. HURTA ET AL.: "Early induction of ribonucleotide reductase gene expression by transforming growth factor beta1 in malignant H-ras transformed cell lines." THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 35, 15 December 1991, pages 24097-24100, XP002053309 cited in the application see the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 97/ 00540

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 19 to 25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see continuation-sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2, 11-18 (partially) and 3-6 (completely)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-2, 11-18 {partially} and 3-6 {completely}

An antisense oligonucleotide having a sequence which is complementary to a nucleic acid sequence from a ribonucleotide reductase R2 gene, pharmaceutical compositions comprising the said antisense oligonucleotide, use of the said antisense oligonucleotide to prepare a medicament, DNA sequences comprising a transcriptional initiation region and sequence encoding said antisense oligonucleotide and vectors comprising said DNA.

2. Claims: 1-2, 11-18 {partially} and 7-9 {completely}

An antisense oligonucleotide having a sequence which is complementary to a nucleic acid sequence from a ribonucleotide reductase R1 gene, pharmaceutical compositions comprising the said antisense oligonucleotide, use of the said antisense oligonucleotide to prepare a medicament, DNA sequences comprising a transcriptional initiation region and sequence encoding said antisense oligonucleotide and vectors comprising said DNA.

3. Claim : 26

A method of evaluating if a compound inhibits transcription or translation of a ribonucleotide reductase gene comprising transfecting a cell with an expression vector comprising a recombinant molecule comprising a nucleic acid sequence encoding a ribonucleotide reductase and the necessary elements for the transcritpion or translation of the nucleic acid.

4. Claim : 27

Method of evaluating a compound for its ability to regulate a Ras signalling pathway by assaying for an agonist or antagonist of the interaction of R2 and Raf-1 and/or Rac-1.